EDITORIAL

Respiratory influences on oxygen transport and exercise performance in health and disease

Transport of O_2 from inspired air to the mitochondria in contracting skeletal muscle requires a coordinated interaction of several physiological systems. The respiratory system is typically considered to be responsible for the first two steps in O_2 transport – namely, the bulk movement of O_2 in atmospheric air to alveoli (ventilation) and the transfer of O_2 from alveolar gas to capillary blood in the lungs (diffusion). However, it is increasingly appreciated that the respiratory system may impact on systemic O_2 transport via direct, mechanical effects on cardiac output and indirect, reflex effects on muscle blood flow and its regional distribution. Insufficient O_2 transport to working muscles increases the reliance on anaerobic energy systems, thereby facilitating the accumulation of metabolites. In turn, the development of contractile dysfunction (peripheral fatigue) is accelerated, with a corresponding increase in the activation of metaboreceptor afferents and a reduction in the neural drive to locomotor muscles (central fatigue). These respiratory influences on O_2 transport and exercise performance may be relatively minor in healthy individuals exercising at sea-level, but are likely to gain in relative importance as fitness level rises. Respiratory influences are also likely to gain in importance, even at submaximal exercise intensities, in healthy individuals in the hypoxia of high altitude and in a significant number of patients with cardiorespiratory disease.

In this issue of *Experimental Physiology*, we present reports from a symposium entitled 'Respiratory influences on oxygen transport and exercise performance in health and disease' that was held on 10 July 2019 at the annual meeting of The Physiological Society in Aberdeen, UK. The reports highlight recent work pertaining to the role of the respiratory

system in limiting O_2 transport and how these respiratory influences might compromise exercise performance in healthy individuals and in patients with chronic heart and/or lung disease.

In their report, Sheel, Taylor, and Katayama (2020) emphasise recent findings in healthy humans that show a significant influence of sympathetic vasoconstrictor activity, mediated by both respiratory and locomotor muscle metaboreceptors during intense endurance exercise, on the constraint of blood flow and O_2 transport to both sets of muscles. Experimentally increasing the work of breathing was found to elicit reductions in blood flow to inactive and active limb muscles during submaximal exercise, but only if the work of breathing was of a sufficient magnitude. Reducing the work of breathing by using a mechanical ventilator during intense exercise was found to increase blood flow to inspiratory muscles and to decrease blood flow to active limb muscles. Together, these findings support the concept of a significant influence of respiratory muscle work on the distribution of blood flow to both respiratory and locomotor muscles. More recently, reducing the normally occurring work of breathing during exercise was shown to decrease sympathetic nerve activity to non-involved muscles. This latter finding lends support to the notion of a 'respiratory muscle metaboreflex', whereby high respiratory muscle work increases metaboreceptor afferent activity, which in turn increases sympathetic outflow, eliciting a redistribution of blood flow.

In endurance-trained athletes capable of working at high cardiac outputs, excessive rises in pulmonary artery and capillary pressures and a limited pulmonary vascular reserve appear to place a disproportionate load on the right heart. These excessive increases in pulmonary vascular pressures may reduce O_2 transport via reductions in stroke volume and impairments in pulmonary gas exchange. Increases in pulmonary vascular pressure are also likely to be important in older adults and especially in patients with cardiovascular disease. In their

report, Taylor, Shapiro, and Johnson (2020) discuss the impact of pulmonary hypertension on the pulmonary haemodynamic response to exercise in patients with heart failure. Emphasis is placed on the causes of exercise limitation in two distinct subsets of pulmonary hypertension: (1) isolated postcapillary pulmonary hypertension; and (2) combined pre- and postcapillary pulmonary hypertension. The authors provide evidence that pulmonary hypertension contributes to exercise limitation in heart failure through a substantial increase in right ventricular afterload that restricts right ventricular contractile reserve and forward flow of blood from the right ventricle to the pulmonary vasculature and systemic circulation.

Cystic fibrosis is an autosomal recessive condition caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR protein is expressed in multiple organs and, thus, this complex condition could pose significant limitations to central and localised O_2 delivery as well as the ability to effectively extract and utilise O_2 at the myocyte level, even when pulmonary function is preserved. Saynor, Gruet, Rodriguez-Miguelez, and Harris (2020) review the central and peripheral contributors of cystic fibrosis pathophysiology that modulate the dynamic balance between O_2 delivery and utilisation during exercise. The authors emphasise recent evidence showing that, at the mild end of the disease spectrum and at low intensities of exercise, the human body has the ability

to physiologically compensate for some degree of dysfunction in an effort to maintain the metabolic demands of low-intensity exercise. With more severe dysfunction and more intense exercise, however, a pharmacological ‘helping hand’ may be needed to improve exercise performance.

In contrast to most untrained healthy individuals, the respiratory system in patients with chronic obstructive pulmonary disease (COPD) may present significant challenges to

systemic O_2 transport and exercise performance. In their report, Vogiatzis, Louvaris, and Wagner (2020) discuss blood flow regulation during exercise in health and COPD. Using an indicator-dilution method, the authors have shown that blood flow to the intercostal region trends toward, or even falls below, resting values during intense exercise and that these dramatic reductions in flow are even more marked in COPD *versus* health. The authors attribute the apparent reductions in intercostal blood flow during exercise to mechanical compression of vessels within the muscle or to redistribution of blood flow within the respiratory muscles. Further insight into the priority of blood flow distribution during exercise in humans will require advances in techniques for the quantification of blood flow to diaphragm muscle.

The symposium reports that feature in this issue of *Experimental Physiology* provide important new insights into how the respiratory system may influence O_2 transport and exercise performance in health and disease. The reports have much to offer by way of informing our understanding of the limitations to human performance and the development of effective interventions.

COMPETING INTERESTS

None.

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